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Editorial

Liver stiffness values in healthy subjects: Implications for clinical practice ☆

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Liver stiffness measurement (LSM) using transient elastography is considered a promising technique for the assessment of severity of chronic liver disease, having been shown in a number of disease settings to be correlated with the fibrosis stage as assessed histologically [1–4]. Although a number of studies have included groups of subjects without evidence of fibrosis histologically, none has examined the range of liver stiffness values in a cohort of healthy subjects. The paper by Roulot and colleagues in this edition of the Journal examines a large cohort of subjects with no evidence of liver disease to establish estimates for normal values and to investigate possible factors in the apparently normal population, which may affect the LSM [5].

In previously published multivariate analyses of cohorts of patients with chronic liver disease, fibrosis was found to be the only factor to correlate significantly with increasing LSM [1,2,6]. However, the authors of the original proof-of-principle *in vitro* study recognised that a single physical parameter (i.e. stiffness) was unlikely to describe fully a complex biological system in which fibrosis is just one part [7]. Subsequent studies have demonstrated that portal pressures, as assessed by the hepatic venous pressure gradient (HVPG) [8] and inflammation, as assessed by the histological necro-inflammatory grade [9] also correlate with liver stiffness. Indeed, a paper by Pinzani's group has demonstrated an increase of LSM in the cirrhotic range in patients with acute viral hepatitis with no history of liver disease and, furthermore, reduction of liver stiffness, corresponding to biochemical improvement of the hepatitis [10]. The effect of steatosis on LSM has not been investigated in depth, although histological evidence of steatosis has not been found to affect liver stiffness on multivariate analysis of cohorts of patients with chronic liver disease.

The knowledge that factors other than fibrosis affect liver stiffness makes analysis of subjects in whom there is no fibrosis all the more relevant. Roulot and colleagues examined a cohort of apparently healthy individuals attending a free health check. This study has considerable strengths. The population studied exceeded 400 subjects, making it by far the largest study of liver stiffness in "normal" individuals. LSMs were acquired according to published criteria, by a single operator who was blinded to the clinical data. By taking a population of subjects attending a health check, rigorous clinical and biological data collection was attainable from subjects, who could be classified as healthy on the basis of exclusion of factors predisposing to, or associated with, liver disease. In addition, the diagnosis of metabolic syndrome used validated diagnostic criteria.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; HVPG, hepatic venous pressure gradient.

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However, imaging of the liver was not reported to exclude structural abnormalities. In addition, assessment of cardiovascular health (apart from the presence of hypertension) and in particular, the presence of a degree of congestive heart failure was not reported. From a physiological perspective, congestive cardiac failure causes hepatic venous congestion, which is likely to cause an increase in LSM and, as such, may be a highly relevant confounding factor in subjects with the metabolic syndrome. In addition, as this was a free health check, there may have been a selection bias in that those subjects attending may have had symptoms, which triggered attendance.

Using the 5th and 95th centiles from the non-obese population, normal values were tentatively estimated at between 3.3–7.8 kPa in women and 3.8–8.0 kPa in men. This fits with previous work in which the cut-off value for significant fibrosis ($F \geqslant 2$) was considered to be 8.8 kPa (1). It was also found that liver stiffness was higher in men than in women, in obese subjects than lean subjects, and in those with the metabolic syndrome, compared to those without the metabolic syndrome. The metabolic syndrome was diagnosed in 59 of 429 subjects analysed. In these subjects, the liver stiffness was found to be significantly higher than in those without the metabolic syndrome, when accounting for age and sex. Unsurprisingly, those with the condition were much more likely to be obese than those without, although on multivariate analysis accounting for body mass index (BMI), the metabolic syndrome was still a major determinant of higher liver stiffness values. Despite this difference, 88% of those with the metabolic syndrome had LSMs within the defined normal range for those without the condition. This implies that there may be no clear role for LSM in the diagnosis of the metabolic syndrome. It also suggests that the normal ranges for LSM may have to be shifted in different disease populations and raises a general note of caution when interpreting individual LSM results in isolation. In 4 of the 7 subjects with the metabolic syndrome and LSM > 8 kPa, liver biopsy was performed, demonstrating NASH with fibrosis stage F2 and steatosis involving <10% of the hepatocytes. This was said to support the hypothesis that isolated steatosis does not increase liver stiffness. It might be preferable to state that this information does not disprove the hypothesis, as the effect of isolated steatosis on liver stiffness measurement has not been tested specifically in a cohort stratified primarily by degree of hepatic steatosis, for example by using proton magnetic resonance spectroscopy [11].

Satisfactory LSM was not possible in a quarter of obese individuals (BMI > 30 kg/m^2) and in 88% of those with a BMI > 40 kg/m^2. These patients were, by necessity, excluded from the study but would be likely to have hepatic steatosis: their liver stiffness may differ from the remainder of the cohort. This is something that might be assessed by MR elastography [12,13], or by development of different probes designed for obese subjects.

This study brings forward substantially the knowledge of liver stiffness values in the normal population, which may form a basis for future clinical practice. However, a number of issues warrant further investigation. In this study, the mean BMI of the population studied was 25.6 kg/m^2. If LSM increases with BMI, as was asserted by Roulot and colleagues, the exportability of concrete normal ranges may not be universal. For example, in the Dallas Heart study of over 2000 individuals, the mean BMI was >30 kg/m^2 in a population where the mean age was comparable [14]. In such a population, the failure rate for data acquisition is likely to be substantially higher than that reported here, and the normal ranges may apply to a smaller proportion of the population. The applicability of the technique in these circumstances should be investigated further and may entail modification of transient elastography hardware. In addition, racial differences have not been reported. Distribution of body fat varies with race [15,16], and this may affect rates of successful LSM acquisition with implications for the normal values used in areas of high ethnic diversity.

The possibility of using LSM as a screening tool for liver disease in the general population has also been raised. The technique is certainly safe and acceptable to patients, and is relatively cheap when used on a large scale. However, the relationship between liver stiffness and the pathogenesis of liver disease is still unclear. It is not possible to explain confidently the cause of a high LSM, since the actual or potential effects of haemodynamic changes including portal hypertension [8], hepatic inflammation [10,17], and steatosis have to be borne in mind in addition to fibrosis [2,4]. Nevertheless, LSMs may serve as a trigger for further investigation, as a stiff liver is seldom found in the absence of any pathology. The liver stiffness threshold to trigger further investigation is open to debate and should take into account the demographics of the population to be screened, the likely prevalence of the condition to be screened for, and the acceptability of subsequent investigations, both to the subject and from the perspective of resource allocation. LSM might be used as a screening tool in a subpopulation at high risk of chronic liver disease, such as those of South Asian origin living in the UK (where there may be potential NAFLD in those with the metabolic syndrome [18]), or those with a history of intravenous drug usage, who have a high risk of viral hepatitis. In such instances, the normal ranges within these populations should be assessed and defined appropriately.

The paper by Roulot and colleagues represents the first reported large scale attempt to define the normal range of liver-stiffness measurements and this will surely form the basis of attempts to widen the usage of LSM beyond those with pre-defined chronic liver disease.

However, it is likely that different populations will require different cut-off values for normal ranges and isolated LSM values still need to be interpreted in individual patients in the context of other tests.

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